At this point, military service during World War I interrupted Warburg's research. When he resumed it, he characterized *Atmungsferment* more like an enzyme and focused on how it could be inhibited, first by hydrogen cyanide (Warburg, 1925b) and later by carbon monoxide (Warburg, 1929). Although he could not isolate the enzyme, he developed techniques to fingerprint it by its absorption spectrum. Throughout this period, though, he emphasized that the critical operation involved the activation of oxygen. He fiercely opposed Wieland's contention that removal of hydrogen atoms was the crucial step in oxidation and that dehydrogenases operated on the substrate to activate and remove pairs of hydrogen atoms.

The competing theories of Wieland and Warburg each offered a simple mechanism to explain cellular respiration – one operation activated a molecule, which then reacted with the other molecule (removing it from the substrate if necessary). Their alternative accounts became the focus of a bitter controversy as each party maintained that he had identified *the* critical operation. However, other researchers began to consider the possibility that both processes were involved in cellular respiration. As proposed by Albert Szent-Györgyi (1924), "In cellular oxidation the *activated hydrogen* is burned by the *activated oxygen*. In the terminology of the hydrogen activation theory this means that molecular oxygen is not a hydrogen acceptor; the biological hydrogen acceptor is the oxygen activated in Warburg's system" (Szent-Györgyi, 1924, p. 196, translated by Fruton, 1972, p. 322). On this proposal, the claims of Wieland and Warburg did not intrinsically conflict but instead, as Figure 3.13 shows in skeletal form, figured at opposite ends of the same pathway.

As it turned out, however, the mechanism was far more complex than one obtained by simply combining the two proposals. Working from both ends of the pathway, researchers in the 1920s and 1930s identified a multitude of operations that linked them into a complex mechanism. (Bechtel and Richardson, 1993, characterized this as a move from *simple localization* to *complex localization*.) Thunberg himself took the first step by proposing the idea of a sequence of dehydrogenation reactions in which the product of a given dehydrogenation was further dehydrogenated (or otherwise operated on) in another reaction.[43] In particular, he proposed the following

[43] Thunberg actually had the idea of a sequences of reactions as early as 1913, before he encountered Wieland's conception of dehydrogenation: "The oxidative processes in the living cell must be thought of as forming chain reactions, a series of reactions connected to one another in such a way that, by and large, none of the links in the reaction chain can proceed more rapidly than the others" (1913, translated in Holmes, 1986, p. 68).